SUMMARY FOR BASIS OF APPROVAL

I. IDENTIFICATION OF DRUG

PLA Ref. No. 88-0660

Drug Licensed Name: **Aldesleukin**

Drug Trade Name: **Proleukin®**

Manufacturer: **Chiron Corporation**
4560 Horton Street
Emeryville, California 94608

Date of Approval: May 5, 1992

II. INDICATION FOR USE:

Aldesleukin is indicated for the treatment of adults (≥ 18 years of age) with metastatic renal cell carcinoma. Studies have shown that aldesleukin can induce durable complete or partial responses in a subset of such patients.

Careful patient selection is mandatory prior to administration of aldesleukin. Therapy with aldesleukin should be restricted to patients with normal cardiac and pulmonary functions as defined by thallium stress testing and formal pulmonary function testing. See contraindications, warnings, and precautions sections of the package insert for more details regarding patient screening.

Evaluation of clinical studies to date reveals that patients with more favorable ECOG Performance Status (ECOG PS 0, asymptomatic) at initiation of aldesleukin therapy are more likely to experience tumor responses and less likely to experience several serious toxicities than are patients with poorer performance status. Therefore, selection of patients for treatment should include assessment of performance status. Experience in patients with PS > 1 is extremely limited.

Aldesleukin should not be administered to patients who have previously experienced specific adverse reactions to aldesleukin which are listed in the Contraindications section of the package insert.

III. DOSAGE FORMS, ROUTE OF ADMINISTRATION AND RECOMMENDED DOSAGE

Aldesleukin is supplied as a sterile white to off-white, preservative-free, lyophilized powder packaged in single-use vials intended for intravenous administration after reconstitution and dilution. Each vial contains 22 million IU (1.3 mg) and should be reconstituted aseptically with 1.2 ml of Sterile Water for Injection, USP. When reconstituted as directed, each ml contains 18 million IU (1.1 mg) aldesleukin, 50 mg mannitol and 0.18 mg sodium dodecyl sulfate (SDS), buffered with approximately 0.17 mg monobasic sodium phosphate and 0.89 mg dibasic sodium phosphate to pH 7.5. Proleukin for Injection is supplied in packs of ten individually-boxed single-use vials. The product contains no preservative.

After reconstitution and prior to infusion, the dose of aldesleukin should be diluted in 50 ml of 5% Dextrose Injection, USP. Aldesleukin should not be mixed with other drugs. The presence of human serum albumin (HSA) in the diluent has been shown to alter aldesleukin's pharmacokinetics in humans and its pharmacokinetics and toxicology in animals and is therefore not recommended. Dilution or reconstitution with Bacteriostatic Water for Injection, USP, or 0.9% Sodium Chloride Injection, USP should be avoided because of increased aldesleukin aggregation. The use of polyvinyl chloride (PVC) bags is recommended for dilution and infusion since it results in more consistent drug delivery than does the use of glass bottles.

Aldesleukin is administered by 15-minute intravenous infusion every eight hours.

The following schedule has been used to treat adult patients with metastatic renal cell carcinoma. Each course of treatment consists of two 5-day treatment cycles separated by a rest period.

> 600,000 IU/kg (0.037 mg/kg) administered every eight hours by a 15 minute intravenous infusion for 14 doses. Following nine days of rest, the schedule is repeated for another 14 doses, for a total of 28 doses per course.

During clinical trials, doses were frequently held for toxicity. Patients treated with this schedule received a median of 20 of the 28 doses during the first course of therapy.

Patients should be evaluated for response approximately four weeks after completion of a course of therapy and again immediately prior to the scheduled start of the next course. Additional courses of treatment may be given to patients only if there is some tumor shrinkage following the preceding course, and if retreatment is not contraindicated (see package insert). Each treatment course should be separated by a rest period of at least seven weeks from the date of hospital discharge. Tumors have continued to regress up to 12 months following initiation of aldesleukin therapy.

IV. MANUFACTURING AND CONTROLS

A. Manufacturing and Controls

Aldesleukin is a hydrophobic protein produced by recombinant DNA technology. Aldesleukin, des-alanyl-1, ser-125 recombinant human interleukin-2 is expressed in E. coli. The process for manufacture begins with fermentation of the Working Cell Stock, a strain of E. coli carrying the IL-2 gene. Following fermentation, the culture is harvested, and RIL-2 is extracted into a buffered solution containing sodium dodecyl sulfate (SDS). After a series of steps involving reduction, size exclusion chromatography, and oxidation, the protein is further purified by large scale reversed phase high performance liquid chromatography (RP-HPLC) and concentrated by precipitation. The resulting paste is solubilized with a 1% SDS solution. After further purification via a size exclusion chromatographic step, the purified IL-2 solution is diafiltered at physiological pH to reduce the SDS concentration. Mannitol and phosphate buffer are added to the diafiltered solution to adjust the concentration of IL-2. The formulated product is sterile-filtered, aseptically filled into glass vials and lyophilized.

A Master Cell Stock is produced from the parent culture E. coli MM 294-1/pLW 45, then put into sterile cryotubes, labeled and cryogenically frozen and stored in liquid nitrogen. A Working Cell Stock is produced from the Master Cell Stock through fermentation; it is then harvested, dispensed into sterile polycarbonate bottles, labeled and stored at a maximum of -70°C. Both cell stocks are tested periodically for purity, viability and plasmid retention.

Raw materials and packaging components to be used in the production of aldesleukin are subjected to appropriate quality control evaluations before they are accepted for use in manufacture.

A number of assays are used to characterize aldesleukin and ensure product quality and consistency on a lot to lot basis. The sequence of aldesleukin has been verified by amino acid sequencing and tryptic peptide map analysis. Each lot of product is monitored for identity by tryptic peptide map analysis and N-terminal sequencing. Purity is analyzed by non-reducing and reducing SDS-polyacrylamide gel electrophoresis (SDS-PAGE), RP-HPLC, and isoelectric focusing. Potency is determined by a lymphocyte proliferation bioassay using a potency standard which has been cross-referenced against the World Health Organization 1st International Standard for IL-2 and is expressed in International Units (IU) as defined by that standard. The relationship between potency and protein mass is as follows: 18×10^6 IU = 1.1 mg protein. Each lot of aldesleukin must pass tests for sterility, general safety, LAL for bacterial endotoxin, plasmid DNA and host E. coli antigen.

Upon reconstitution, aldesleukin exists as biologically active, non-covalently bound microaggregates with an average size of 27 recombinant interleukin-2 molecules. A turbidimetric analysis is employed to determine the mean size of aldesleukin microaggregates in the aldesleukin solution and must fall within preset specifications to ensure consistency. Additionally, the amount of protein pelletable by centrifugation is assayed for each lot.

As a result of variation in diafiltration, final lots of aldesleukin may vary in SDS concentration within a prespecified acceptance range.

B. Stability Studies

The 18 month dating period for aldesleukin at the recommended storage conditions, refrigerated at 2 to 8°C (36 to 46°F), is supported by the results of stability studies. Three lots of product were stored at the recommended temperature and above for 24 months and an additional four lots were stored for 18 months. At the recommended temperature, aldesleukin retained biological activity, purity and quality for 18 months. Stability studies are ongoing.

Over the 18 months period, small changes have been observed in the RP-HPLC profile indicating accumulation of a minor variant(s) and or a degradation product(s). In order to assess the significance of these findings, clinical data were analyzed in regard to the storage period of the aldesleukin prior to use. A significant portion of the aldesleukin administered in clinical trials had been stored between 12 and 18 months and no effect on efficacy or safety could be found as a function of time of storage. Separate control specifications for the

RP-HPLC profile have been established for the time of lot release (to ensure consistency of production) and for stability testing (to ensure that stability does not change from that observed in material used in clinical trials). No other testing, including SDS-PAGE, has indicated any product change during storage as recommended.

C. Validation

Utility systems, manufacturing equipment, manufacturing processes and analytical methodologies used in the production of aldesleukin have been validated according to established written procedures. Procedures are in place to ensure the regular maintenance of equipment and the regular monitoring of environmental conditions within the production facilities.

D. Labeling

The labels, cartons and package insert are in compliance with the applicable regulations (21 CFR 201.56, 201.57, 610.60, 610.61 and 610.62). The product trademark, Proleukin®, is not known to conflict with any other drug product trademark.

E. Establishment Inspection

A prelicensing inspection of the Cetus/Chiron manufacturing facility where aldesleukin is produced was conducted by personnel from the Center for Biologics Evaluation and Research on October 8 to 11, 1991. Facilities and procedures were found to be in compliance with current Good Manufacturing Practices.

F. Environmental Impact Assessment

An Environmental Impact Assessment Report dated October 30, 1991 was submitted by Cetus Corporation as part of the establishment and product license applications. The production facility complies with the standards set forth by the United States Environmental Protection Agency, the State of California, the local county and the city of Emeryville for the introduction of waste substances into the environment. No adverse impact on the environment is expected to result from the production or distribution of aldesleukin. A finding of no significant impact is attached.

V. PHARMACOLOGY

A. Pharmacological Activities

Interleukin-2 plays a central role in the regulation of immune system functions including the activation and proliferation of lymphocytes of various types. Early studies in murine tumor systems demonstrated the potential of native IL-2 as an anti-cancer agent, both as a single agent and in combination with in vitro activated immune cells. Aldesleukin has been shown to possess immunological activities similar to those observed with native IL-2: growth and

activation of T lymphocytes, induction of natural killer (NK) cell activity, and induction of lymphokine activated killer (LAK) cell activity.

The precise mechanisms of the anti-tumor activity of IL-2 have not been defined. Similar pharmacologic effects have been observed in rodents, sheep and humans. Widespread lymphoid proliferation is observed, which is dependent on both dose level and duration of treatment. With prolonged treatment, infiltrating immune cells can be identified in nearly all major organ systems. Since IL-2 induces a widespread activation of immune system functions, including a number of other lymphokines and cytokines, it has not been possible to identify precisely which factors are responsible for the anti-tumor activity.

B. Pharmacokinetics and Biodistribution

1. Animal Data

The pharmacokinetic characteristics of aldesleukin were studied in rats and sheep, biodistribution in rats.

Pharmacokinetic studies indicated that approximately 30% of the dose of aldesleukin administered by intravenous infusion can be found to distribute initially to the plasma. Thus, the apparent volume of the central compartment was considerably larger than the plasma volume in all species tested. By contrast, plasma concentrations of a monomeric preparation of IL-2 lacking SDS were about 2-fold higher than the plasma concentrations of the same dose of aldesleukin and the volume of the central compartment approximated the plasma volume for this preparation. Conversely, a visibly aggregated preparation of IL-2 containing less SDS than aldesleukin resulted in initial plasma concentrations up to 50-fold lower.

Studies have demonstrated that aldesleukin in the plasma is primarily cleared by metabolism to amino acids in the cells lining the proximal convoluted tubules of the kidneys. The clearance rate for aldesleukin were about 5-fold faster in rats than in humans. Plasma IL-2 concentrations were proportional to dose level over a 100-fold dose range, and repeated doses (7 and 14 days) were cleared at the same rate as a single dose in rats.

To determine the fate of majority of infused aldesleukin which cannot be recovered from the plasma, a biodistribution study was performed in rats. This showed that aldesleukin distributed quite extensively to the liver, the lungs and kidney within the first 30 seconds of infusion. On the other hand, a monomeric preparation of IL-2 lacking SDS distributed preferentially only to the kidney.

Pelletable material resulting from centrifugation of aldesleukin was tested in rats. Results demonstrated that approximately 10% of the dose was recovered as IL-2 in the circulation compared to administration of the same dose of aldesleukin, and this material was cleared from plasma at a rate similar to non-pelletable IL-2.

In sheep the overall α half life of aldesleukin was 13.4 minutes, the β half life, 80.1 minutes. These compared to observed human values of 13.8 minutes and 85 minutes, respectively.

2. Human Data

Data from 52 cancer patients given a five minute intravenous bolus injection demonstrated that the α half life of aldesleukin was 13.8 minutes, the β half life, 85 minutes. Additional data from nine patients, four of whom received the drug in glass bottles containing 5% HSA in normal saline and five patients who received it in Viaflex bags containing 0.1% HSA in D5W indicated that the α half life ranged from 6.2 to 17.2 minutes. Recovery of administered dose in the systemic circulation of these patients was 34.1%, suggesting rapid distribution outside the plasma volume as observed in sheep and rats.

3. Effects of diluent and vessel

Three delivery systems were studied in the sheep: D5W without HSA in PVC bags, D5W and 0.1% HSA in bags, and normal saline and 5% HSA in glass bottles. The percent dose recovered in the systemic circulation was lower in the group in which HSA was not used (20.9%) than in the other two groups (26.2% and 27.1%, respectively). This difference appeared to result not from loss of aldesleukin in the delivery system in that comparable amounts of aldesleukin could be recovered from the delivery system. Rather, a larger volume of the central compartment (lower recovery in plasma) was observed when HSA was not used.

In the CD rat, an even larger HSA effect was observed. Use of HSA in the infusate was associated with increased plasma levels and decreased volume of the central compartment by approximately 2-fold.

In one pharmacokinetic study in humans, D5W and 0.1% HSA in PVC bags was compared with normal saline and 5.0% HSA in glass bottles. No significant differences were observed. In a second study, three systems were compared: D5W without HSA in PVC bags, D5W without HSA in glass bottles, and normal saline with 5% HSA in glass bottles. In vitro recovery of IL-2 from the infusate from glass bottles lacking HSA was significantly lower than recovery from glass bottles containing HSA or from PVC bags lacking HSA. For glass bottles without HSA, in vitro loss of recoverable IL-2 bioactivity was approximately 50% and was more marked than loss of IL-2 immunoreactive protein measured by ELISA. While significant effects of vessel on *in vitro* recovery had not been observed in other studies, trends toward lower recovery with glass bottles had been observed.

C. Toxicity Studies

1. Acute Toxicity

Acute toxicity of aldesleukin was evaluated in rats. A single intravenous injection of 12.5 mg/kg aldesleukin or excipient was given to ten rats of each sex. All rats survived the 14 days observation period, and no toxicities were observed.

2. Subacute Toxicity

Subacute toxicity studies of aldesleukin were done in mice, rats, rabbits and sheep.

Mice were injected intravenously with aldesleukin, 0.95 mg/kg or saline for five days/week for two weeks (10 males/group). All animals survived treatment and the additional 14 days observation period, and no toxicities were observed.

Six subacute studies were done in rats.

Study 1. Rats were injected intravenously with 1 mg/kg/day aldesleukin, excipient or saline for five days/week for two weeks (10 males and 10 females/group). Half the animals were sacrificed on day 13; the remainder were allowed to recover and were sacrificed on study day 26.

Study 2. Rats were injected intravenously for 11 consecutive days with 0.5, 1.0, 2.0 or 4.0 mg/kg/day aldesleukin or excipient (control). There were five males and females/group.

Study 3. Rats received aldesleukin by continuous intravenous infusion for ten days. Groups of four males and four females/group received aldesleukin at 0.074, 0.110, or 0.146 mg/kg/day or excipient (control).

Study 4. Rats were administered aldesleukin intravenously at dose levels of 10 µg/kg t.i.d., 50 µg/kg t.i.d. or 1.0 mg/kg once/day or excipient (ccntrol) t.i.d. for seven consecutive days. Each group had five males and five females.

Study 5. Rats received either aldesleukin or a solution of the pelleted material resulting from centrifugation of aldesleukin by intravenous injection t.i.d. for seven days to determine the pharmacological properties of the pelletable component of aldesleukin. Dose levels for both preparations were 10 or 50 µg/kg/day. Control rats received excipient. Each group had five males and five females.

Study 6. Rats were administered aldesleukin without HSA or with 0.1% HSA in D5W by intravenous infusion daily for 14 days. Dose of aldesleukin was 0.5 or 1.0 mg/kg/day. The control rats received 0.1% HSA in D5W. Each group had ten males and ten females.

These studies in rats indicated that repeated administration of aldesleukin resulted in signs of hepatotoxicity, pulmonary interstitial inflammation, decreased serum albumin, thrombocytopenia and anemia. Pharmacologic responses induced by aldesleukin included leukocytosis, lymphocytosis, eosinophilia, extramedullary hematopoiesis and hepatosplenomegaly. In study 1, the rats had recovered at 26 days, and hematological and biochemical parameters were within normal limits. Spleen weights were still elevated, but most microscopic findings were normal. Study 5 with pelletable material showed that the toxicological profile of the pelletable material was qualitatively comparable to aldesleukin, but that the severity and/or incidence of toxicities were less pronounced than those observed with aldesleukin treatment (in-life through gross necropsy observation).

Data from Study 6 indicated that the incidence of mortality was significantly higher in the rats receiving aldesleukin in D5W and HSA than in those receiving aldesleukin in D5W alone. At the dose levels tested, no major differences in types of toxicity which were observed.

Two subacute studies were done in rabbits.

Study 1. Rabbits received 0.77 mg/kg/day aldesleukin or saline (control) intravenously five days a week for two weeks, then were observed for two additional weeks. Groups had ten males each.

Study 2. Rabbits received aldesleukin intravenously for five days a week for two weeks. Groups of five males and five females received 1 mg/kg aldesleukin/day or excipient or saline. Half the animals were sacrificed on study day 13, the remainder on study day 26.

In the first study, all aldesleukin rabbits survived, and two control rabbits died. Three rabbits in the aldesleukin group had local reactions at the injection site. In the second study, toxicologic and pharmacologic results were similar to those obtained in rats at day 13.

By study day 26, blood cell counts and liver function tests had generally returned to normal, but spleen and liver weights were still elevated. Seven deaths occurred in the second study; three deaths were considered to be related to the test article, while the others were due to infectious disease or traumatic injury.

Three sheep were treated with aldesleukin, 100 ug/kg twice a day by 30 minute intravenous infusion at a six hour interval for five days, and three received excipient by the same schedule. Sheep receiving aldesleukin developed decreases in systemic vascular resistance accompanied by an increase in cardiac output and heart rate, increased capillary permeability, fever, decreased PO_2 and slight pulmonary hypertension.

3. Teratology and Reproductive Toxicology

One Segment II study has been done in rats to evaluate the effect of aldesleukin on the pregnant female and embryo.

The Segment II study had four groups of 25 animals each. Pregnant rats received aldesleukin intravenously on days six through 15 of presumed gestation at 0.5, 1.0 or 2.0 mg/kg/day; the control group received excipient. The study ended on day 20 of presumed gestation. Drug induced mortality was observed at all three dose levels of aldesleukin. Drug related clinical observations and necropsy observations were similar to those seen in the subacute rat studies. There were no drug-related changes in litter mean for corpora lutea, implantations, litter sizes, percent resorbed conceptuses or the number of dams with any resorptions. No fetal malformations or variations were reported with aldesleukin doses up to 2.0 mg/kg/day.

4. Sodium dodecyl sulfate (SDS) toxicity

A subacute study was performed in rabbits to assess the toxicity of SDS, a solubilizing agent present in aldesleukin. Rabbits simultaneously received intravenous and intramuscular injections of SDS or phosphate buffered saline for ten consecutive days. Dose/day of SDS per injection was 0.01, 0.25 or 1.0 mg/kg. Local irritation was observed with both routes of administration. Systemic effects of treatment were not observed, even at the highest combined dose of 2.0 mg/kg/day. One rabbit died at the high dose of SDS, but the reason for death was unclear.

D. Effect of SDS concentration in the product

Table 1 summarizes results of product testing and rat pharmacokinetic testing using lots of aldesleukin-like material intentionally manufactured with varying diafiltration to result in wide variations of SDS concentration. As can be seen, SDS concentrations below approximately 100 ug/ml were associated with in increased turbidity and lower plasma levels at one hour. SDS concentrated at 200 ug/mg and above were associated with lower turbidity (consistent with monomeric IL-2 at SDS of 1086); however, unlike monomeric IL-2 preparations lacking SDS (see section V.B.1), the high SDS preparation did not result in increased plasma levels.

Table 1. Test Results from Aldesleukin-like Preparations with varying SDS Concentrations

SDS (μg/mg)	Turbidity (cm^2/g)	Pelletable Protein (%)	Bioactivity ($x10^6$ IU/mg)	Plasma IL-2 at 1 h (ng/ml)
25	0.9	97	20	<1
65	5.1	2	18	12
95	1.0	1	18	16
125	0.6	1	21	24
157	0.6	2	20	26
197	0.3	1	22	30
1086	0.03	1	16	23

Additionally, aldesleukin-like preparations with varying SDS concentrations (65, 125, 165, 204, and 1086 μg SDS/ mg protein) were tested in BDF_1 mice bearing B16 melanoma artificial lung metastases. IL-2 was administered in doses ranging from 1 to 15 mg/kg/dose iv qd for 7 days beginning 3 days after tumor cell inoculation. No difference could be detected in tumor response among preparations tested. However, drug induced mortality was significantly higher with the preparations containing 1086, 65, and 125 μg/kg than with the other two preparations. Aldesleukin preparations with 165 and 204 μg/mg of SDS induced minimal mortality at the doses tested.

The acceptance range for SDS in final lot aldesleukin has been set at 160 - 195 μg SDS/ mg protein. Variation within this acceptance range has not been correlated with variability in outcome in clinical studies and has not been shown to impact significantly upon results of product tests **in vitro** or **in vivo**. However, studies of SDS variability of aldesleukin in animal models are ongoing.

VI. MEDICAL

A. Synopses of Seven Clinical Trials Supporting this Application

Based on the animal studies demonstrating anti-tumor activity of IL-2, studies in patients with renal cell carcinoma were undertaken, initially using a combination of IL-2 and LAK cells. Initial success with this therapeutic regimen led to further studies using IL-2 alone.
All 255 patients in these trials had metastatic or unresectable renal cell carcinoma. Aldesleukin was administered to all patients by 15 minute intravenous infusion q8h for 5 days (up to 14 doses, as tolerated). After 6 to 10 days off drugs, patients received an additional 5 days of therapy. Doses were withheld based upon patient tolerance. Patients with stable or responding tumors were eligible for additional courses of therapy every two months.

In all studies reported, a complete response is defined as complete disappearance of all malignant disease for at least four weeks. Partial response is defined as ≥50% decrease in the surface area of measured tumor, documented on two occasions at least four weeks apart, without appearance of new lesions or enlargement of any existing lesion by ≥25%.

One or more of the following aspects of aldesleukin infusion varied within each trial: the use of normal saline vs. D5W, the use of HSA, the use of glass bottles vs. PVC bags. The effects of these variables are briefly summarized in the combined analysis (section VI.B.3).

Table 2. Clinical studies

STUDY	1	2	3	4	5	6	7
DOSE (15 min. iv inf. q8h)							
IU/kg (x 10^5)	6	6	7.2	6	7.2	6	6
Days	1-5	1- 5	1- 5	1- 5	1- 5	1- 5	1- 5
	15-19	11-15	14-19	11-15	14-18	12-16	12-16
DEMOGRAPHICS							
Median Age	54	51	52	54	50	46	51
Median time from Dx(mo.)	6.5	12.3	10.7	11.1	9.9	8.5	13.8
Prior nephrectomy	85%	84%	95%	78%	85%	75%	100%
RESULTS - All patients							
N	71	63	41	37	27	8	8
CRs	3	1	4	0	1	0	0
PRs	8	8	6	3	3	0	0
PS=0							
N	51	38	30	22	17	4	4
CRs	3	1	4	0	1	0	0
PRs	7	5	5	2	2	0	0
Drug-related Deaths	0	7	2	2	0	0	0

Study 1. This was a multi-center, open-label study with patients randomly assigned to treatment with aldesleukin alone or with aldesleukin plus interferon α. Only the patients receiving aldesleukin alone are included in this data summary.

Two patients had responses lasting longer than one year. Nine of the responders were still in remission, and all were still alive five to 19 months after starting therapy.

Study 2. This was a multi-center, open-label, single arm study of aldesleukin.

One patient had a response lasting 23 months. Eight of the responders were still in remission, and all were still alive from four to 24 months after treatment began.

Of seven deaths on-study that were probably related to treatment with aldesleukin, one was attributed to myocardial infarction, two were due to infectious complications, one to a gastrointestinal bleed, two to pulmonary complications, and one to unknown causes.

Study 3. This was a single-center, open-label study with patients randomly assigned to treatment with aldesleukin alone or aldesleukin in conjunction with systemic administration of LAK cells.

This was the first study initiated with aldesleukin, and the follow-up is much longer than other studies. Duration of response was more than a year for nine of the ten responders, and four were still on-going at 32, 43 , 49 and 50 months when the data were analyzed. Eight of the ten patients were still alive 35 to 54 months after beginning treatment.

Two drug-related deaths occurred, one of myocardial infarction, the other of bowel perforation and sepsis.

Study 4. This was a multi-center study, open-label, with patients randomly assigned to receive aldesleukin alone or aldesleukin with LAK cells. Only patients receiving aldesleukin alone are included in this data summary.

Two patients had responses lasting more than a year. Two responders were still in remission, and three remained alive 11 to 23 months after treatment initiation.

Two drug-related deaths occurred, one due to cardiac tamponade, the other due to pulmonary complications.

Study 5. This was a single-center, open-label study with patients randomly assigned to receive aldesleukin alone or aldesleukin in conjunction with polyethylene glycol-IL-2. Only patients receiving aldesleukin alone are included in this application.

All responding patients were still in remission at last data analysis and were still alive seven to 14 months after starting therapy. None of the patient responses were more than one year, as this was a more recent study.

Study 6. This was a single-center, single-arm, open-label study.

Study 7. This was a single-center, single-arm, open-label study.

B. Summary of Clinical Data

1. Efficacy

A total 255 patients pooled from a total of seven clinical studies with metastatic renal cell carcinoma were included in the aldesleukin database for patients receiving high dose therapy by 15 minute i.v. infusion every eight hours. Median age of the patient population

was 52 (18 to 71 years). Seventy percent of the patients were males. Sixty-five percent had PS 0 according to ECOG criteria; 31% had PS 1, and 4% had PS 2 or more. The median time from diagnosis of renal cell carcinoma to treatment was 8.5 months, and 56% were diagnosed within 12 months of therapy with aldesleukin. Eighty-five percent of patients had prior nephrectomy, while prior chemotherapy was uncommon (3%).

All seven studies used similar treatment schedules, differing only in the durations of the rest period between the two five day treatment intervals, and the interval between courses. Two studies used 720,000 IU/kg/dose (68 patients), and the others used 600,000 IU/kg/dose (187 patients). Dosing was administered every eight hours until dose-limiting toxicity was encountered; then doses were withheld until toxicities resolved. Although protocols indicated 28 to 30 doses were to be given per course of therapy, in practice most patients received fewer doses due to toxicity (median 15 of 28 scheduled doses in course 1 for 720,000 IU/kg regimen and 20 of 28 doses for 600,000 IU/kg regimen). No maintenance therapy was given.

Several demographic and baseline variables were analyzed to determine if any were predictive of response in an attempt to find selection procedures that could lead to an improved therapeutic index. Of the analyses performed, performance status was found to be the primary predictor of both response and survival. With improved performance status, response rates increased and incidence of slow-to-resolve serious toxicities was lower.

Overall response rates are summarized in Table 3.

Table 3. Pooled Analysis of Clinical Studies

Response rates	N	CR	PR	CR + PR
600,000 IU/kg (0.037 mg/kg)	187	4 (2%)	19 (10%)	23 (12%)
720,000 IU/kg (0.044 mg/kg)	68	5 (7%)	9 (13%)	14 (20%)
PS=0	166	9 (5%)	21 (13%)	30 (18%)
PS=1	80	0 (0%)	7 (9%)	7 (9%)
PS=2	9	0 (0%)	0 (0%)	0 (0%)
All 7 studies	255	9 (4%)	28 (11%)	37 (15%)
95% confidence interval				(11-20%)

Of the 28 partial responses, 19 remained in partial response at last data analysis (duration of response ranging from 1 to 43 months) and 9 had relapsed (duration of response 3 to 28 months). The projected median duration of partial responses is 19 months. Fifteen of the 28 partial responders had greater than 90% reduction in the sum of the cross-sectional area of their index lesions.

The nine complete responders had complete response durations of 50+, 49+, 32+, 23+, 17, 13+, 10+, 3+, and 1+ months where a "+" indicates an ongoing response at last follow-up.

Seven of the 28 partial responders and none of the complete responders were symptomatic from their disease (PS=1) at study entry. Of these seven patients, one returned to baseline after therapy and the other six became asymptomatic (PS=0).

Due to the absence of an internal control, analysis of survival data was not of great value in assessing efficacy.

2. Safety

The rate of drug related deaths on single-agent aldesleukin in the seven studies was 4% (11/255). Toxicity was primarily associated with a capillary leak syndrome and required intensive management. Nearly all patients had doses of aldesleukin withheld due to severe toxicity.

Adverse reactions were usually, but not invariably, reversible within two to three days of discontinuation of therapy. The median duration from last dose to hospital discharge was 3 days. However, at one week after therapy, 14% of patients remained hospitalized, most commonly due to infection, or to GI perforation and/or bleed. In 166 patients for whom detailed, validated toxicity data were available at the time of analysis, persistent non-fatal toxicities included two cases of myocardial infarction - one associated with endocarditis and leading to valve replacement and coronary artery bypass graft, two cases of renal failure requiring dialysis for at least one month, five cases requiring laparotomy - three for bleeding and two for perforation, six patients requiring intubation lasting over one week, two cases of gangrene requiring surgery - one below-the-knee amputation, and a cerebrovascular accident without long-term sequelae.

The most serious adverse reactions were generally more common in patients with PS=1 than with PS=0 as noted in Table 4.

Table 4. Incidence of Select Adverse Reactions by Performance Status

ECOG PS	Deaths	Intubation	Gangrene	Coma	GI bleed	Sepsis
0	4%	8%	0%	1%	4%	6%
1	6%	25%	6%	6%	8%	18%

The incidences of reported adverse events in 373 patients (255 with renal cell carcinoma and 118 with other metastatic malignancies) treated with the high dose q8h 15 minute infusion regimen of aldesleukin are summarized in Table 5.

Table 5. Incidence of Adverse Events

Events by body system	% of Patients
Cardiovascular	
Hypotension	85
(requiring pressors)	71
Sinus Tachycardia	70
Arrhythmias	22
Atrial	8
Supraventricular	5
Ventricular	3
Junctional	1
Bradycardia	7
Premature Ventricular Contractions	5
Premature Atrial Contractions	4
Myocardial Ischemia	3
Myocardial Infarction	2
Cardiac Arrest	2
Congestive Heart Failure	1
Myocarditis	1
Stroke	1
Gangrene	1
Pericardial Effusion	1
Endocarditis	1
Thrombosis	1
Pulmonary	
Pulmonary Congestion	54
Dyspnea	52
Pulmonary Edema	10
Respiratory Failure leading to intubation	9
Tachypnea	8
Pleural Effusion	7
Wheezing	6
Apnea	1
Pneumothorax	1
Hemoptysis	1
Gastrointestinal	
Nausea and Vomiting	87
Diarrhea	76
Stomatitis	32
Anorexia	27
GI Bleeding	13
(requiring surgery)	2
Dyspepsia	7
Constipation	5
Intestinal Perforation/Ileus	2
Pancreatitis	<1
Neurologic	
Mental Status Changes	73
Dizziness	17
Sensory Dysfunction	10
Special Sensory Disorders (vision, speech, taste)	7
Syncope	3
Motor Dysfunction	2
Coma	1
Seizure (grand mal)	1
Renal	
Oliguria/Anuria	76
BUN Elevation	63
Serum Creatinine Elevation	61
Proteinuria	12
Hematuria	9
Dysuria	3
Renal Impairment Requiring Dialysis	2
Urinary Retention	1
Urinary Frequency	1
Hepatic	
Elevated Bilirubin	64
Elevated Transaminase	56
Elevated Alkaline Phosphate	56
Jaundice	11
Ascites	4

Hepatomegaly	1

Hematologic

Anemia	77
Thrombocytopenia	64
Leukopenia	34
Coagulation Disorders	10
Leukocytosis	9
Eosinophilia	6

Abnormal Laboratory Findings

Hypomagnesemia	16
Acidosis	16
Hypocalcemia	15
Hypophosphatemia	11
Hypokalemia	9
Hyperuricemia	9
Hypoalbuminemia	8
Hypoproteinemia	7
Hyponatremia	4
Hyperkalemia	4
Alkalosis	4
Hypoglycemia	2
Hyperglycemia	2
Hypocholesterolemia	1
Hypercalcemia	1
Hypernatremia	1
Hyperphosphatemia	1

Dermatologic

Pruritus	48
Erythema	41
Rash	26
Dry Skin	15
Exfoliative Dermatitis	14
Purpura/Petechiae	4
Urticaria	2
Alopecia	1

Musculoskeletal

Arthralgia	6
Myalgia	6
Arthritis	1
Muscle Spasm	1

Endocrine

Hypothyroidism	<1

General

Fever and/or Chills	89
Pain (all sites)	54
Abdominal	15
Chest	12
Back	9
Fatigue/Weakness/Malaise	53
Edema	47
Infection (including urinary tract, injection site, catheter tip, phlebitis, sepsis)	23
Weight Gain (10%)	23
Headache	12
Weight Loss (10%)	5
Conjunctivitis	4
Injection Site Reactions	3
Allergic Reactions (non-anaphylactic)	1

Serious adverse events not included above which were less frequently (<1%) observed in trials involving more than 1800 patients treated with aldesleukin-based regimens in investigational studies included liver or renal failure resulting in death; duodenal ulceration; fatal intestinal perforation; bowel necrosis; fatal cardiac arrest, myocarditis, and supraventricular tachycardia; permanent or transient blindness secondary to optic neuritis; fatal malignant hyperthermia; pulmonary edema resulting in death; respiratory arrest; fatal respiratory failure; fatal stroke; transient ischemic attack; meningitis; cerebral edema; pericarditis; allergic interstitial nephritis; tracheo-esophageal fistula; fatal pulmonary emboli; and severe depression leading to suicide.

Immunogenicity: Fifty seven of 77 (74%) of renal cancer patients treated with the every eight hour aldesleukin regimen developed low titers of non-neutralizing anti-interleukin-2 antibodies. Neutralizing antibodies were not detected in this group of patients, but have been detected in 1/106 (1%) of patients treated with intravenous aldesleukin using a wide variety of schedules and doses. The clinical significance of anti-interleukin-2 antibodies is unknown. Some patients with anti-interleukin-2 antibodies have received further therapy and the presence of antibodies is not currently considered a contraindication for therapy.

3. Regimen and Method of Administration

In these studies, IL-2 was infused at two doses, 600,000 IU/kg or 720,000 IU/kg, in normal saline, D5W, D5W with 0.1% HSA, or D5W with 5% HSA, using PVC bags or glass bottles. In general, more infusions were tolerated in patients receiving the lower dose. No significant effect of dose, diluent, or vessel on response or mortality rate was observed; however numbers in many groups were low. It is recommended that aldesleukin be administered at 600,000 IU/kg/dose in PVC bags in D5W without HSA for the following reasons.

- The largest experience (98 of 255 patients) was with 600,000 IU/kg, D5W without HSA in plastic bags and was representative of the total experience.
- Toxicology data indicated a higher mortality in rats when HSA was present in the infusion (see section IV.B.2).
- Pharmacokinetic data suggest decreased recovery of aldesleukin from glass bottles without HSA as compared with bottles with HSA or PVC bags with or without HSA (see section IV.C.3)
- Solubility data indicate decreased solubility in normal saline without HSA.

4. Concluding Discussions

Studies in 255 patients with metastatic renal cell carcinoma demonstrated an overall response rate of 15%, 4% complete responses and 11% partial responses. Eight of nine complete responders remained in remission at last analysis, after 1 to 50 months of follow-up; median duration of partial responses, many of which consisted of over 90% tumor shrinkage, was 19 months. Toxicity during treatment with aldesleukin was severe but usually reversed rapidly after treatment was withheld. Toxicity was primarily associated with an aldesleukin-induced capillary leak syndrome and required intensive management. The adverse effects were usually not chronic or cumulative, and the patients were discharged from the hospital a median of three days after completing the first course of therapy. However, persistent serious toxicities

occurred in a small percent of patients and the on-study mortality rate was 4%. Patients had been carefully selected for good physiological status. A performance status of 0 by ECOG criteria (i.e., asymptomatic) was associated with higher response rates and lower toxicities. It was concluded that the benefits offered by treatment with aldesleukin outweighed the risks of therapy for selected patients.

C. Advisory Committee Considerations:

On July 30, 1990, members of the Biological Response Modifiers (BRM) Advisory Committee met and reviewed the data provided by Cetus Corporation for patients with metastatic renal cell carcinoma treated with aldesleukin by continuous infusion or 15 minute bolus every eight hours. The members requested that additional analyses be done to define a patient population which would benefit from therapy with aldesleukin.

On January 17, 1992, Chiron Corporation (formerly Cetus Corporation) again met with the BRM Advisory Committee. Data on additional patients were provided, as well as long-term follow-up data for patients reported in 1990. Retrospective and prospective data analyses demonstrated that patients with a performance status of 0 had higher response rates and fewer severe adverse reactions. Additional data demonstrated that the continuous infusion regimen was associated with inferior response rates and this regimen was no longer proposed for approval. Data regarding aldesleukin aggregates and choice of diluents were also presented. It was the consensus of the committee that efficacy and safety data were adequate to support licensure of the every 8 hour infusion regimen, that labelling should warn strongly of the higher rates of serious adverse events observed in patients with a performance status of 1, that HSA should not be used in the diluent in the indication, and that Chiron should pursue vigorous investigative efforts regarding microaggregates and choice of diluents.

D. Adequacy of New Drug Labeling:

Based on the results presented in this submission, it is concluded that Interleukin-2, when administered in accordance with the package insert, is safe and effective in the treatment of adults (> 18 years old) with metastatic renal cell carcinoma.

VIII. PHASE IV TRIALS REQUIRED FOR LICENSURE

A. Additional animal studies to determine the extent to which the variations in the SDS concentration across the range of product specifications may impact the pharmacology of aldesleukin.

B. Additional animal studies to evaluate further the impact of the use of HSA on the toxicology of aldesleukin and its potential relevance to humans.

C. Studies to determine the effects of antibodies and elevated creatinine on the pharmacokinetics of aldesleukin in humans.

D. Investigation into patient characteristics which may identify patients likely to benefit from aldesleukin.

E. Ongoing follow-up on tumor response and survival data from responders in the database of 255 patients described herein.